At page 1, line 2 (after the Title of the Invention), please insert:

A1 --Related Applications

This application is a divisional application of U.S. Application Serial No. 09/036,327, filed March 6, 1998, now allowed.- -

At page 4, please replace the paragraph beginning at line 24 with the following paragraph:

A2 Synthetic inhibitors of FBPase have also been reported. Maryanoff reported that fructose-2,6-bisphosphate analogs inhibit FBPase by binding to the substrate site. J. Am. Chem. Soc., 106:7851 (1984); U.S. Patent No. 4,968,790 (1984). These compounds, however, were relatively weak and did not inhibit glucose production in hepatocytes presumably due to poor cell penetration.

At page 6, please replace the paragraph that begins at line 11 with the following paragraph:

A3 FIG. 11B shows the intracellular generation of compound **2.7** in rat hepatocytes treated with compound **16.4**, a prodrug, to inhibit glucose production in rat hepatocytes.

At page 6, please replace the paragraph that begins at line 21 with the following paragraph:

A4 Gruber et al. U.S. patent application Serial Number 08/355,836 , now issued U.S. Patent No. 5,658,889 described the use of inhibitors of the AMP site of FBPase to treat diabetes.

At page 9, lines 9-10, please delete the sentence beginning "The term "alkylsulfonate" . . ."

At page 11, line 2, please replace the first two paragraphs, which begin at lines 1 and 4, with the following two paragraphs:

The term alkoxyalkylaryl refers to the group -alk-O-alk-aryl- wherein each "alk" is independently an alkylene group. "Lower alkoxyalkylaryl" refers to such groups where the alkylene group is lower alkyl.

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The term "alkylacylaminoalkyl" refers to the group -alk-N-(COR)-alk- where each alk is an independently selected alkylene group. In "lower alkylacylaminoalkyl" the alkylene groups are lower alkyl.

At page 12, please replace the paragraph that begins at line 1 with the following paragraph:

The term "aminocarboxamidoalkyl" refers to the group -NH-C(O)-N(R)-R wherein each R is an independently selected alkyl group. "Lower aminocarboxamidoalkyl" refers to such groups wherein each R is lower alkyl.

A6

At page 12, please replace the paragraph that begins at line 9 with the following paragraph:

The term "guanidino" refers to both -NR-C(NR)-NR_2 as well as -N=$C(NR_2)_2$ where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

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At page 12, please replace the paragraph that begins at line 12 with the following paragraph:

The term "amidino" refers to -C(NR)-NR_2 where each R group is independently selected from the group of -H, alkyl, alkenyl, alkynyl, aryl, and alicyclic, all optionally substituted.

A8

At page 15, please replace the paragraph that begins at line 7 with the following paragraph:

[6] Thio-containing phosphonate ester prodrugs have been described that are useful in the delivery of FBPase inhibitors to hepatocytes. These phosphonate ester prodrugs contain a protected thioethyl moiety as shown in formula E. One or more of the oxygens of the phosphonate can be esterified. Since the mechanism that results in de-esterification requires the generation of a free thiolate, a variety of thiol protecting groups are possible. For example, the

A9

A9 disulfide is reduced by a reductase-mediated process (Puech et al., Antiviral Res., 22: 155-174 (1993)). Thioesters will also generate free thiolates after esterase-mediated hydrolysis. Benzaria, et al., J. Med. Chem., 39:4958 (1996). Cyclic analogs are also possible and were shown to liberate phosphonate in isolated rat hepatocytes. The cyclic disulfide shown below has not been previously described and is novel.

At page 18, please replace the paragraph that begins at line 23 with the following paragraph:

A10 X group nomenclature as used herein in formula 1 describes the group attached to the phosphonate and ends with the group attached to the 6-position of the purine ring. For example, when X is alkylamino, the following structure is intended:

At page 28, please replace the paragraph that begins at line 1 with the following paragraph:

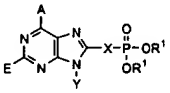
A11 Bis-(4-acetoxyphenyl) esters;

At page 30, please replace the paragraph at line 4 with the following paragraph:

A12 Bis-(bis-2-hydroxyethylamidomethyl) esters.

At page 42, please replace the table that begins on line 1 with the following table:

A13

Table Compound No.	Synthetic Example No.				
269		NH2	F	cyclopropylmethyl	2,5-furanyl
270		NH2	Cl	cyclopropylmethyl	2,5-furanyl
271		NH2	Br	cyclopropylmethyl	2,5-furanyl
272		NH2	Et	cyclopropylmethyl	2,5-furanyl
273		NH2	CN	cyclopropylmethyl	2,5-furanyl
274		NH2	Me	cyclopropylmethyl	CONHCH2
275		NH2	SMe	cyclopropylmethyl	CONHCH2

276		NH2	F	cyclopropylmethyl	CONHCH2
277		NH2	Cl	cyclopropylmethyl	CONHCH2
278		NH2	Br	cyclopropylmethyl	CONHCH2
279		NH2	Et	cyclopropylmethyl	CONHCH2
280		NH2	CN	cyclopropylmethyl	CONHCH2
281		NH2	Me	cyclopropylmethyl	NHCOCH2
282		NH2	SMe	cyclopropylmethyl	NHCOCH2
283		NH2	F	cyclopropylmethyl	NHCOCH2
284		NH2	Cl	cyclopropylmethyl	NHCOCH2
285		NH2	Br	cyclopropylmethyl	NHCOCH2
286		NH2	Et	cyclopropylmethyl	NHCOCH2
287		NH2	CN	cyclopropylmethyl	NHCOCH2
288	2.18	NH2	H	3-(1-imidazolylpropyl)	2,5-furanyl
289	19.1	NH2	H	neopentyl	1,2-C6H4-O-
290	21.1	NH2	H	2-phenethyl	CONHCH2

A13

At page 45, please replace the paragraph that begins at line 23 with the following paragraph:

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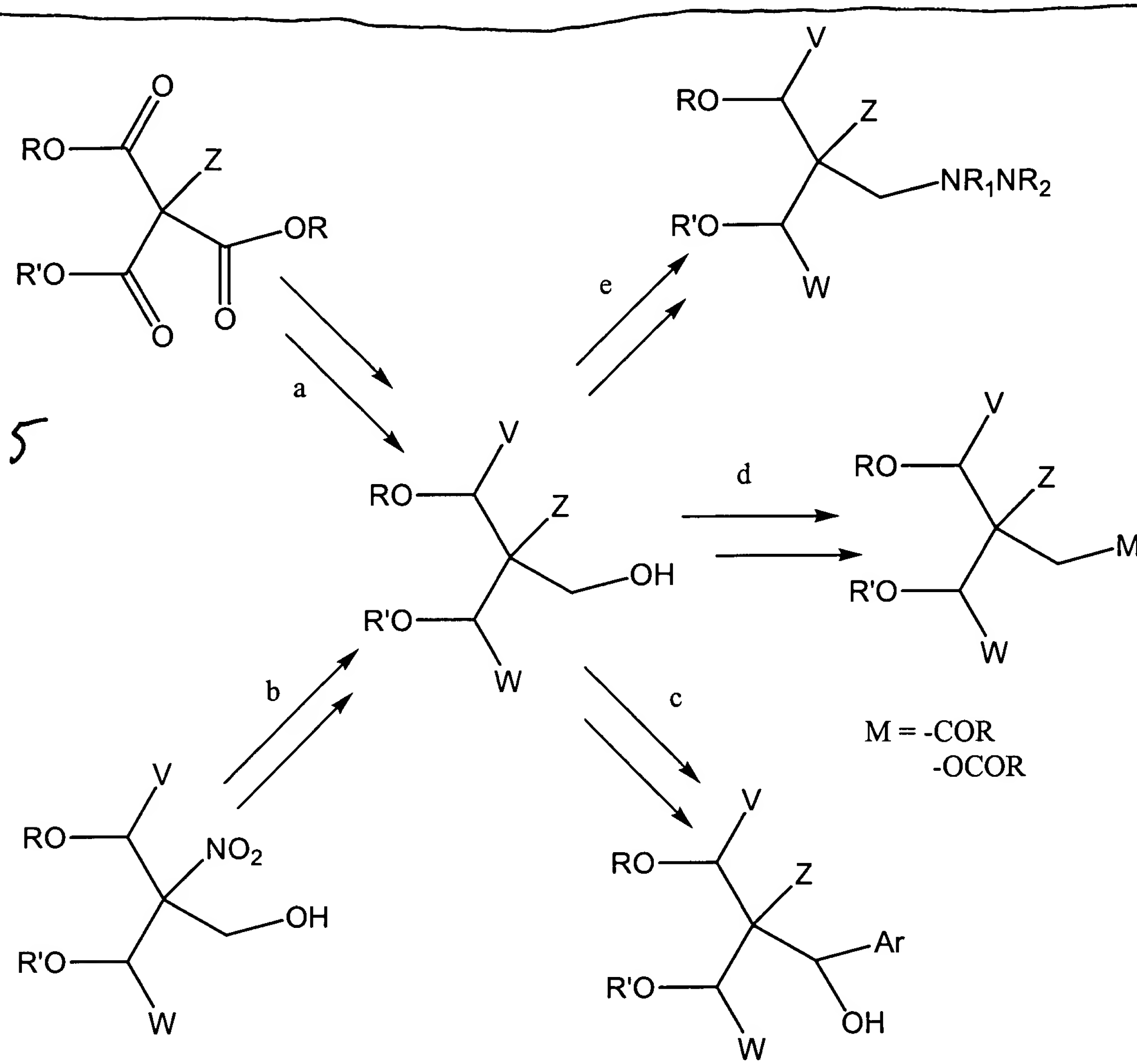
Such reactive dichlorophosphonate intermediates can be prepared from the corresponding phosphonic acids and the chlorinating agents e.g. thionyl chloride (Starrett, et al, *J. Med. Chem.*, **1994**, 1857), oxalyl chloride (Stowell, et al, *Tetrahedron Lett.*, **1990**, *31*: 3261), and phosphorus pentachloride (Quast, et al, *Synthesis*, **1974**, 490). Alternatively, these dichlorophosphonates can also be generated from disilyl phosphonate esters (Bhongle, et al, *Synth. Commun.*, **1987**, *17*: 1071) and dialkyl phosphonate esters (Still, et al, *Tetrahedron Lett.*, **1983**, *24*: 4405; Patois, et al, *Bull. Soc. Chim. Fr.*, **1993**, *130*: 485).

At page 49, please replace the reaction scheme that appears immediately after line 2 with the following reaction scheme:

A15



At page 68, please replace the paragraph that begins at line 10 with the following paragraph:

A16

Step A. A mixture of N^9-phenethyl-8-bromoadenine (1 mmol), tetrakis (triphenylphosphine)palladium (0.05 mmol), and triethylamine (5 mmol) in DMF in a sealed tube was warmed at 110 °C under 50 psi of carbon monoxide. After 24 h the cooled reaction mixture was evaporated and purified through chromatography to give N^9-phenethyl-8-methoxycarbonyladenine as a yellow solid. TLC: Rf= 0.12, 5 % MeOH-CH_2Cl_2.

At page 81, please replace the paragraph that begins at line 10 with the following paragraph:

A17

Step A. A solution of 2-amino-4,6-dichloropyrimidine (1 mmol), neopentylamine (1.05 mmol), and triethylamine (2 mmol) in n-butanol was stirred at 110 °C for 12 h. Extraction and chromatography gave 2-amino-4-chloro-6-neopentylpyrimidine as a yellow solid. TLC: $R_f = 0.2$, 30 % EtOAc-hexane.

At page 83, please replace the paragraph that begins at line 27 with the following paragraph:

A18

Following the above described procedures, other cyclic esters are also prepared, such as N^9-neopentyl-8-(2-(5-(2-(methoxycarbonyloxymethyl)-propan-1,3 -yl)phosphono)furanyl)adenine, N^9-neopentyl-8-(2-(5-(2-(hydroxymethyl)-propan-1,3 -yl)phosphono)furanyl)adenine, N^9-neopentyl-8-(2-(5-(2,2-dihydroxymethylpropan-1,3 -yl)phosphono)furanyl)adenine, N^9-neopentyl-8-(2-(5-(2-(methoxycarbonyloxymethyl)propan-1,3 -yl)phosphono)-furanyl)adenine is prepared by coupling N^9-neopentyl-8-(2-(5-phosphono)-furanyl)adenine with 2-(methoxycarbonyloxymethyl)-1,3-propanediol which was prepared as follows:

At page 85, please replace the paragraph that begins at line 9 with the following paragraph:

A19

A mixture of N^9-neopentyl-8-(2-(5-phosphono)furanyl)adenine (1 mmol) and tris(hydroxymethyl)aminomethane (1.05 mmol) in methanol is stirred at 25 °C for 24 h. Evaporation gives N^9-neopentyl-8-(2-(5-phosphono)furanyl)adenine tris(hydroxymethyl)aminomethane salt.

At page 85, please replace the paragraph that begins at line 13 with the following paragraph:

A20

Examples of the methods of the present invention include the following. It will be understood that these examples are exemplary and that the method of the invention is not limited solely to these examples.

At page 85, please replace the paragraph that begins at line 21 with the following paragraph: